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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/937,636 | 01/22/2002 | Eric Wen Su | X-12652 | 2380 |

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| EXAMINER | |
|---|---|
| O HARA, EILEEN B | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

DATE MAILED: 12/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/937,636 | SU ET AL. | |
| | Examiner | Art Unit | |
| | Eileen O'Hara | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *22-39* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Advisory Information*

1.1 The numbering of claims is not in accordance with 37 CFR 1.126, which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). The original claims as filed were 1-29. The preliminary amendment canceled claims 1-21 and added claims 22-31. Claims 22-31 of the preliminary amendment were renumbererd 30-39.

1.2 Claims 26-29, 38 and 39 encompass a pharmaceutical composition and method of treating with the pharmaceutical composition, whereas the composition comprises as an active ingredient a composition as claimed in claim 4 or 12. Claims 4 and 12 have been canceled. Additionally, claim 12 is a composition comprising at least one polypeptide of any of claims 8-11, but claim 8 is drawn to a transgenic animal. The Examiner believes that incorporation of claim 8 in claim 12 is in error, and claims 26-29 are being interpreted as compositions comprising the polypeptides of SEQ ID NO: 3 or 4, with claim 26 depending from claim 22. If Applicants intend otherwise, this should be addressed in the response to this Office Action.

### *Claims Status*

2. Claims 22-39 are pending in the instant application. A copy of the renumbered claims is attached to this Office Action for the convenience of the Applicants.

***Election/Restrictions***

3. Applicant's election with traverse of Group I in the reply filed on Oct. 5, 2004 is acknowledged. The traversal is on the ground(s) that the subject matter of the required search is sufficiently small and closely related as to be capable of examination. This is not found persuasive because the search and examination of gene therapy requires a separate search beyond that of the nucleic acids to determine the enablement of the method, which constitutes separate search and consideration.

The search for Group II would not constitute a separate search, and is therefore rejoined with Group I.

The requirement is still deemed proper and is therefore made FINAL.

All claims are currently under examination.

***Claim Objections***

4.1 Claims 26-29, 38 and 39 are objected to because of the following informalities: they depend from canceled claims.

4.2 Claim 32 is objected to because it encompasses a vector comprising "at least one" nucleic acid according to claim 30, and claim 30 recites "an isolated hOB-BP2h nucleic acid". Appropriate correction is required.

***Priority***

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

***Specification***

6.1 The disclosure is objected to because of the following informalities: there are blanks on page 16, lines 20-22, in reference to the ATCC Deposit.

Appropriate correction is required.

6.2 Applicants are advised that the word "protrein-2" has been changed in the title to "protein-2" to correct the spelling.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7.1 Claims 23 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 23 and 27 encompass methods of treating obesity and associated diseases comprising administering a

polypeptide comprising an amino acid sequence at least 70% identical to an amino acid sequence of SEQ ID NO: 3 or 4, or by administering an antagonist to the proteins. The instant application on page 2 teaches that ob/ob mice mice have a deficiency in leptin and are grossly obese and develop diabetes mellitus, and injection of leptin causes the mice to curb their food intake and shed fat, and that leptin is a poor pharmaceutical due to short half-life in the circulation, and that it is unstable in solution formulations. The instant application teaches that the proteins of SEQ ID NOS: 3 and 4 are leptin-binding proteins, and it is implied that these leptin-binding proteins may effectively increase the plasma half-life of circulating leptin and/or improve physical stability. However, the prior art and the instant application are not enabling for the methods of treatment of obesity with the proteins or antagonist to the proteins. There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).
It is acknowledged that the level of skill in the art is high. However, the prior art teaches that the level of leptin is higher in obese individuals than in those with normal weight (Lallone, U.S. Patent No. 5,830,450), so that it would not be expected that by stabilizing leptin weight loss would occur. The art teaches that an individual's propensity to gain weight, and the ability to lose excess weight, is an extremely complex metabolic problem, and is not easily predictable. There are a number of factors that appear to control body weight, and are thought to play role in

modulation of influencing factors such as appetite and satiety, fat storage, and energy output, and this regulation is quite complex. Besides diet and exercise, there are many factors, including race, ethnicity, age, insulin levels and even distribution of body fat, which all contribute to weight control in an individual. (Halford J C; Blundell J E PROGRESS IN DRUG RESEARCH, (2000) 54 25-58, Halford J C, Curr Drug Targets, (2001 Dec) 2 (4) 353-70, Margetic S; Gazzola C; Pegg G G; Hill R A., INTERNATIONAL JOURNAL OF OBESITY AND RELATED METABOLIC DISORDERS, (2002 Nov) 26 (11) 1407-33 and Druce Maralyn; Bloom Stephen, CURRENT OPINION IN CLINICAL NUTRITION AND METABOLIC CARE, (2003 Jul) 6 (4) 361-7.)

The specification provides no data that administration of the leptin-binding proteins could be useful for treating obesity. Additionally, since the prior art teaches that administration of leptin to obese mice results in weight and fat loss, administration of an antagonist to the binding-proteins of the instant application would not be expected to treat obesity. The specification does not provide any working examples of treatment. Thus, the specification fails to teach the skilled artisan how to use the polypeptides therapeutically without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the proteins or antagonists for the above stated purposes.

Due to the large quantity of experimentation necessary to determine if the polypeptides could be used therapeutically, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the

claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

7.2 Claims 22-39 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO: 4 and splice variant lacking an internal fragment of SEQ ID NO: 3, which are disclosed as being leptin-binding proteins. However, the claims as written include polypeptides comprising fragments and homologues, encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO: 4 with it's splice variant, with the instantly disclosed specific activity, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 4 and splice variant SEQ ID NO: 3. Protein function, however, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance. Given the unpredictability of homology comparisons, and

the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. The instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polypeptides and polynucleotides encompassed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 provides for the use of the polypeptides for the manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claim28 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 22, 24-26, 28, 29-34 and 36-39 are rejected under 35 U.S.C. 102(a) as being anticipated by Kikly et al., WO9853840, December 3, 1998 (cited by Applicants).

Claims 22, 24-26, 28, 29-34 and 36-39 encompass polypeptides at least 70% identical to the polypeptide sequences of SEQ ID NOS: 3 or 4, chimeric proteins thereof comprising constant region of an immunoglobulin, pharmaceutical compositions thereof, or isolated polypeptide comprising at least 90-100% of the contiguous amino acids of SEQ ID NO: 3, nucleic acids encoding a protein at least 90-100% of the contiguous amino acids of the protein of SEQ ID NO: 3 and the complement thereof, recombinant vector, host cell, and nucleic acids comprising a polynucleotide having a nucleotide sequence at least 90% identical to a nucleotide sequence encoding a polypeptide comprising a portion of SEQ ID NO: 3, wherein said portion lacks from 30-50 amino acids of the amino terminus, or wherein said portion lacks from 131-171 amino acids from the carboxy-terminus, or said portion includes a combination of any of the amino terminal and carboxy terminal deletions.

The protein of SEQ ID NO: 3 is a splice variant of the protein of SEQ ID NO: 4, having an internal deletion of 127 amino acids, and is therefore 80% identical to the protein of SEQ ID NOS: 4.

Kikly et al. disclose a protein (SEQ ID NO: 2) that is 100% identical to the protein of SEQ ID NO: 4 of the instant application and encoding nucleic acid that is 100% identical to SEQ ID NO: 2 of the instant application. Kikly discloses that this protein is a member of the sialoadhesion family of proteins involved in cell interaction, and also teaches fusion proteins comprising constant region of immunoglobulin (page 29), use of the polypeptides for treatment of conditions and polypeptides present in a pharmaceutical composition (pages 18-21), variant polypeptides that can have deletions (page 26), vectors and host cells (pages 9-12). The protein and nucleic acid of Kikly et al. also comprise isolated polypeptide comprising at least 90-100% of the contiguous amino acids of SEQ ID NO: 3 and nucleic acids encoding a protein at least 90-100% of the contiguous amino acids of the protein of SEQ ID NO: 3. Since claim 36 encompasses a nucleic acid molecule comprising a polynucleotide having a sequence at least 90% identical to a nucleotide sequence encoding the polypeptide of SEQ ID NO: 3 having trunctions, the nucleic acid of Kikly meets the limitations of the claims. Therefore, Kikly et al. anticipates the claims.

***Conclusion***

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner